

Ciba Specialty Chemicals Corporation  
USA

Additives

2451  
8EHQ-0798-14233

Ciba

Via Federal Express  
Confidential

July 30, 1998

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(Attention: Section 8(e) Coordinator)  
Office of Pollution Prevention and Toxics  
Environmental Protection Agency  
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Washington, DC 20460

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Subject: TSCA 8(e) Notice - TKA 40185 (CG37-0609)

Dear Section 8(e) Coordinator:

This letter and the enclosed report contain no Confidential Business Information.

In accordance with EPA's March 16, 1978 Policy Statement on Section 8(e) reporting under the Toxic Substances Control Act, the EPA's June, 1991 TSCA Section 8(e) Reporting Guide, Ciba Specialty Chemicals Corporation wishes to bring to the attention of the Environmental Protection Agency, results seen in an acute oral toxicity study conducted with TKA 40185. TKA 40185 is a research substance being evaluated as a process stabilizer and it is not currently produced domestically. We are enclosing a copy of the study entitled, "Acute Oral Toxicity in Rats RCC Project No. 687126" is enclosed. Clinical signs were observed in the rats, such as hunched posture (2/3 males, no females) and ruffled fur (2/3 males, no females).

Based upon current EPA guidelines, it is felt these results warrant reporting under TSCA 8(e). Please call the undersigned if you have any questions about this submittal.

Cordially,

Ciba Specialty Chemicals Corporation



Naeem Mady, Director,  
Regulatory Compliance



8EHQ-98-14233

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Enclosure: Acute Oral Toxicity in Rats - TKA40185



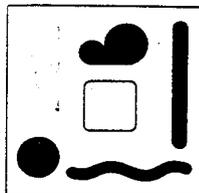
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Value beyond chemistry



**RCC PROJECT 687126**

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**TKA 40185 (CG 37-0609):**

**ACUTE ORAL TOXICITY STUDY IN RATS**

**REPORT**

**Author:** G. Arcelin  
**Sponsor:** CIBA SPECIALTY CHEMICALS INC.  
Additives Division  
P.O. Box  
4002 Basel / Switzerland  
**Study Completion:** 06-APR-1998

Page 1 of 30

**RCC**  
Group

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RCC PROJECT 687126  
TKA 40185

## 1. PREFACE

### 1.1 GENERAL

Title	TKA 40185 (CG 37-0609): Acute Oral Toxicity Study in Rats
Sponsor	CIBA SPECIALTY CHEMICALS INC. Additives Division P.O. Box 4002 Basel / Switzerland
Monitoring Scientist	Dr. P. Dollenmeier
Testing Facility	RCC, Research & Consulting Company Ltd. c/o BRL, Biological Research Laboratories Ltd. Wölferstrasse 4, CH-4414 Füllinsdorf / Switzerland
RCC Project Number	687126
Test Article	TKA 40185 (CG 37-0609)
Test System	Rat

### 1.2 PROJECT STAFF

Study Director	G. Arcelin
Technical Coordinator	R. König

### 1.3 SCHEDULE

Acclimatization	24-FEB-1998 to 02-MAR-1998 (2000 mg/kg, males) 24-FEB-1998 to 03-MAR-1998 (2000 mg/kg, females)
Treatment	03-MAR-1998 04-MAR-1998
Observation	03-MAR-1998 to 17-MAR-1998 04-MAR-1998 to 18-MAR-1998
Termination	17-MAR-1998 18-MAR-1998
Report	06-APR-1998

RCC PROJECT 687126  
TKA 40185

#### **1.4 ARCHIVING**

Research & Consulting Company Ltd., CH-4452 Itingen will archive the following data for at least 10 years:

protocol, report, amendment, raw data and test article reference sample. No data will be discarded without the Sponsor's consent.

RCC PROJECT 687126  
TKA 40185

## 1.5 PROJECT STAFF SIGNATURES

Study Director:

G. Arcelin



Date: 06-APR-98

Management:

(for) T.R. Allen



Date: 06-Apr-1998

RCC PROJECT 687126  
TKA 40185

## 1.6 QUALITY ASSURANCE STATEMENT

RCC, Research & Consulting Company Ltd., CH-4452 Itingen / Switzerland

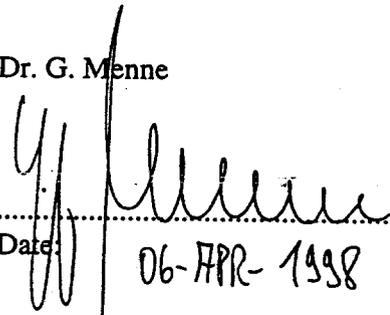
PROJECT NUMBER : 687126  
TEST ARTICLE : TKA 40185  
STUDY DIRECTOR : G. Arcelin  
TITLE : TKA 40185 (CG 37-0609):  
Acute Oral Toxicity Study in Rats

Study procedures were periodically inspected and this report was audited by the RCC Quality Assurance Unit. The dates are given below.

Dates of QAU Inspections / Audits	Dates of Reports to the Study Director and to Management
23-FEB-1998	26-FEB-1998
05-MAR-1998	05-MAR-1998
31-MAR-1998	31-MAR-1998

Manager, Quality Assurance Unit:

Dr. G. Menne

  
Date: 06-APR-1998

RCC PROJECT 687126  
TKA 40185

**GOOD LABORATORY PRACTICE**

**1.7 STATEMENT OF COMPLIANCE / GLP GUIDELINES**

PROJECT NUMBER : 687126  
TEST ARTICLE : TKA 40185  
STUDY DIRECTOR : G. Arcelin  
TITLE : TKA 40185 (CG 37-0609):  
Acute Oral Toxicity Study in Rats

The purity/formulation of the test article and the stability of the test article in the vehicle (PEG 400) are unknown and therefore are excluded from this statement.

This study was conducted in compliance with the following Good Laboratory Practice Regulations:

Good Laboratory Practice (GLP) in Switzerland, Procedures and Principles, March 1986.

OECD Principles of Good Laboratory Practice, Environment Monograph Number 45. OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring - Number 1. Environment Directorate, Organization for Economic Co-operation and Development, Paris 1992.

There were no circumstances that may have affected the quality or integrity of the data.

Study Director:

G. Arcelin



Date:

06-APR-88

RCC PROJECT 687126  
TKA 40185

**1.8 CERTIFICATION OF GLP  
AND VERIFICATION OF THE REPORT**

The statement of Compliance with Good Laboratory Practice found in this report, and signed by the Study Director is truthful and accurate, and this report as provided by the testing facility is complete and unaltered.

Signature of the Sponsor:

*Dollini*  
.....

*April 15, 1998*  
.....

Date:

## **1.9 TEST GUIDELINES**

The study procedures described in this report are based on the following guidelines:

OECD Guidelines for Testing of Chemicals, Number 423 "Acute Oral Toxicity", adopted March 22, 1996.

Directive 96/54/EEC, B.1 tris "Acute Toxicity-Oral-Acute Toxic Class Method", September 30, 1996.

## **1.10 ACCREDITATION**

The testing laboratory "RCC, Research & Consulting Company Ltd." is accredited according to EN 45001 under accreditation number STS 085 by the Swiss Accreditation Service.

## 2. SUMMARY OF RESULTS

Two groups, each using three male or three female HanIbm: WIST (SPF) rats, were treated with TKA 40185 at 2000 mg/kg by oral gavage. The test article was suspended in vehicle (PEG 400) at a concentration of 0.2 g/ml and administered at a volume of 10 ml/kg. The animals were examined for clinical signs four times during test day 1 and once daily during test days 2-15. Mortality/viability were recorded together with clinical signs at the same time intervals. Body weights were recorded on day 1 prior to administration and on days 8 and 15. All animals were necropsied and examined macroscopically.

No deaths occurred during the study.

Clinical signs were observed such as hunched posture and ruffled fur.

The body weight of the animals was within the range commonly recorded for animals of this strain and age.

No macroscopic findings were observed at necropsy.

## 3. CONCLUSION

The median lethal dose of TKA 40185 after single oral administration to rats of both sexes, observed over a period of 14 days, could not be estimated as no death occurred.

**LD<sub>50</sub> : greater than 2000 mg/kg**

## 4. OBJECTIVE

### 4.1 PURPOSE AND RATIONALE

The purpose of this study was to assess the acute oral toxicity of TKA 40185 when administered by single oral gavage to rats, followed by an observation period of 14 days.

This study should provide a rational basis for risk assessment.

## 5. MATERIALS AND METHODS

### Experimental Design

#### 5.1 TEST SYSTEM

Test system	Rat, HanIbm: WIST (SPF)
Rationale	Recognized by the international guidelines as a recommended test system.
Source	BRL, Biological Research Laboratories Ltd. Wölferstrasse 4, CH-4414 Füllinsdorf / Switzerland
Number of animals per group	3 males 3 females
Total number of animals	3 males 3 females
Age when treated	Males: 8 weeks Females: 10 weeks
Body weight range when treated	Males: 189 - 194 g Females: 167 - 186 g
Identification	By unique cage number and corresponding color-coded spots on the tail.
Acclimatization	At least one week under laboratory conditions, after health examination. Only animals without any visible signs of illness were used for the study.

## 5.2 HUSBANDRY

Room no.	101 / BRL
Conditions	<b>Standard Laboratory Conditions</b> Air-conditioned with 10-15 air changes per hour and continuously monitored environment with a target range for room temperature of $22 \pm 3$ °C, and for relative humidity between 40-70 % (values above 70 % during cleaning process possible). The animals were provided with a 12-hour light, 12-hour dark cycle. Music was played during the light period.
Accommodation	Groups of three in Makrolon type-4 cages with standard softwood bedding ("Lignocel", Schill AG, CH-4132 MuttENZ)
Diet	Pelleted standard Kliba 3433, batch no. 94/97 rat maintenance diet (Kliba Mühlen AG, CH-4303 Kaiseraugst) available <i>ad libitum</i> (except for the overnight fasting period prior to intubation). Results of analyses for contaminants are archived at RCC.
Water	Community tap water from Füllinsdorf, available <i>ad libitum</i> . Results of bacteriological, chemical and contaminant analyses are archived at RCC.

## 5.3 TEST ARTICLE (ACCORDING TO INFORMATION PROVIDED BY THE SPONSOR)

Identification	TKA 40185
Product name	CG 37-0609
Description	Violet, solid
Batch number	Mu 53
Purity / Formulation	Unknown, is excluded from the Statement of Compliance.
Stability of test article	Stable under storage conditions; expiration date: January 2000
Stability of test article dilution	Unknown in PEG 400, is excluded from the Statement of Compliance.
Storage conditions	In the original container at room temperature away from direct sunlight.

#### 5.4 TEST ARTICLE PREPARATION

The test article, previously reduced with a mortar and a pestle, was placed into a glass beaker on a tared Mettler PM 460 balance and the vehicle (polyethylene glycol 400) was added. A weight by volume suspension was prepared using a magnetic stirrer as homogenizer. Homogeneity of the test article in the vehicle was maintained during treatment.

During formulation trials performed before the treatment start, the test article was not readily soluble in PEG 400 (suspension, 20% w/v in PEG 400).

The preparation was made shortly before dosing.

#### 5.5 TREATMENT

The animals received a single dose of the test article by oral gavage after being fasted for approximately 18.5 hours, but with free access to water. Food was presented approximately 3 to 4 hours after dosing.

Dosing started with three male animals at the maximum dose of 2000 mg/kg. As no deaths occurred, three female animals were treated at the same dose of 2000 mg/kg.

The application volume was 10 ml/kg body weight.

##### Rationale

Oral administration was chosen because this is one possible route of human exposure during manufacture, handling and use of the test article.

#### 5.6 OBSERVATIONS

##### Mortality / Viability

Four times during test day 1 and once daily during days 2-15.

##### Body weights

On test day 1 (pre-administration), 8 and 15.

##### Clinical signs

Each animal was examined for changes in appearance and behaviour four times during day 1, and once daily during days 2-15. All abnormalities were recorded.

The animals were checked for the clinical signs listed below.  
Findings are detailed in Appendix A.

GENERAL BEHAVIOUR

aggressiveness  
vocalization  
restlessness / excitation  
nervousness, fear  
sedation  
somnolence  
sleep  
coma

RESPIRATION

apnea  
dyspnea  
rales

EYE

chromodacryorrhea  
exophthalmos  
miosis  
mydriasis  
whitish discharge  
lid adhesion  
lacrimation  
negative corneal reflex

MOTOR SUSCEPTIBILITY

spasms  
tonic muscle spasms  
clonic muscle spasms  
opisthotonus  
saltatory spasms  
trismus  
tremor  
muscle-twitching, localized  
muscle-twitching, generalized

NOSE

rhinorrhea  
epistaxis

MOTILITY

akinesia  
ataxia  
dropped head  
hyperkinesia  
hypokinesia  
paralysis, flaccid  
paralysis, spastic  
padding movements  
stiff gait  
rolling movements

BODY POSTURE

ventral body position  
latero-abdominal position  
hunched posture

SKIN

erythema  
edema  
necrosis

VARIOUS

emaciation  
diarrhea  
ruffled fur  
salivation  
pallor  
cyanosis

## 5.7 PATHOLOGY

### NECROPSY

Necropsies were performed by experienced prosectors. At the end of the observation period all animals were sacrificed by intraperitoneal injection of NARCOREN (Rhône Merieux GmbH, D-88471 Laupheim) at a dose of at least 2.0 ml/kg body weight (equivalent to at least 320 mg sodium pentobarbitone/kg body weight). The animals were examined macroscopically and all abnormalities recorded. Thereafter, they were discarded.

## 5.8 STATISTICAL ANALYSIS

No statistical analysis was used as no deaths occurred.

## 5.9 DATA COMPILATION

Body weights were recorded on-line.

Mortality/viability\*, clinical signs and macroscopic findings were compiled into the RCC computer system during recording.

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\* The computerised system does not show that the mortality/viability checks were recorded at the same time as the clinical signs.

## 6. RESULTS

### 6.1 MORTALITY

No deaths occurred during the study.

### 6.2 CLINICAL SIGNS

Group 1 (2000 mg/kg, males): hunched posture (2), ruffled fur (2), no clinical signs (1)

Group 2 (2000mg/kg, females): no clinical signs (3)

( ) = number of animals

See pp. 19-22

### 6.3 BODY WEIGHTS

The body weight of the animals was within the range commonly recorded for animals of this strain and age.

See p. 24

### 6.4 MACROSCOPIC FINDINGS

No macroscopic findings were observed at necropsy.

See pp. 26-27

### 6.5 MEDIAN LETHAL DOSE

The median lethal dose of TKA 40185 after single oral administration to rats of both sexes, observed over a period of 14 days, could not be estimated as no death occurred.

**LD<sub>50</sub> : greater than 2000 mg/kg**

RCC PROJECT 687126  
TKA 40185

## **APPENDIX A**

### **CLINICAL SIGNS**





RCC PROJECT 687126  
TKA 40185

# CLINICAL SIGNS (SUMMARY) MALES

Test day																		
Time after treatment. Hours:	1	1	1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
	1	2	3	5														
GROUP 1 (2000 MG/KG)																		
POSTURE																		
HUNCHED POSTURE.....	(1)	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SKIN / FUR																		
RUFFLED FUR.....	(3)	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-

Median Grades per group / - = sign not observed / . = observation not performed

RCC PROJECT 687126  
TKA 40185

# CLINICAL SIGNS (SUMMARY) FEMALES

Test day Time after treatment. Hours:	1	1	1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
	1	2	3	5														
GROUP 2 (2000 MG/KG) NO CLINICAL SIGNS NOTED																		

Median Grades per group / - = sign not observed / . = observation not performed

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TKA 40185

**APPENDIX B**  
**BODY WEIGHTS**

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TKA 40185

### BODY WEIGHTS (GRAM)

GROUP / SEX	ANIMAL	DAY 1	DAY 8	DAY 15
GROUP 1 / MALES (2000 MG/KG)	1	188.9		
	2	193.0	219.1	237.7
	3	194.4	224.1	256.1
			237.6	265.8
	MEAN	192.1	226.9	253.2
	ST.DEV.	2.9	9.5	14.3
	N	3	3	3
GROUP 2 / FEMALES (2000 MG/KG)	4	186.2		
	5	167.3	212.7	219.6
	6	186.4	189.0	198.6
			207.9	214.1
	MEAN	180.0	203.2	210.8
	ST.DEV.	11.0	12.6	10.9
	N	3	3	3

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TKA 40185

**APPENDIX C**  
**MACROSCOPIC FINDINGS**

RCC PROJECT 687126  
TKA 40185

MACROSCOPIC FINDINGS  
MALES  
GROUP 1 (2000 MG/KG)

ANIMAL 1

(SCHEDULED NECROPSY, 17-MAR-98, DAY 15 AFTER TREATMENT)

NO FINDINGS NOTED

ANIMAL 2

(SCHEDULED NECROPSY, 17-MAR-98, DAY 15 AFTER TREATMENT)

NO FINDINGS NOTED

ANIMAL 3

(SCHEDULED NECROPSY, 17-MAR-98, DAY 15 AFTER TREATMENT)

NO FINDINGS NOTED

RCC PROJECT 687126  
TKA 40185

**MACROSCOPIC FINDINGS**  
**FEMALES**  
**GROUP 2 (2000 MG/KG)**

ANIMAL 4

(SCHEDULED NECROPSY, 18-MAR-98, DAY 15 AFTER TREATMENT)

NO FINDINGS NOTED

ANIMAL 5

(SCHEDULED NECROPSY, 18-MAR-98, DAY 15 AFTER TREATMENT)

NO FINDINGS NOTED

ANIMAL 6

(SCHEDULED NECROPSY, 18-MAR-98, DAY 15 AFTER TREATMENT)

NO FINDINGS NOTED

RCC PROJECT 687126  
TKA 40185

## **APPENDIX D**

### **CERTIFICATION**

- **ACCREDITATION / EUROPEAN STANDARD EN 45001**
- **GLP – CERTIFICATION**

RCC PROJECT 687126  
TKA 40185



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SCHWEIZERISCHER PRÜFSTELLENDIENST  
SERVICE SUISSE D'ESSAI  
SERVIZIO DI PROVA IN SVIZZERA  
SWISS TESTING SERVICE

## ACCREDITATION

### EUROPEAN STANDARD EN 45001

RCC Research & Consulting Company Ltd.  
Zelgliweg 1  
CH-4452 Itingen/BL

This study is performed by the Testing Laboratory for  
the toxicological investigation of  
Pharmaceuticals and Medical Devices, Agrochemicals,  
Industrial Chemicals, Food- and Feed-Additives  
in accordance with

**SN EN 45001**

under accreditation number

**STS 085**

The accredited scope of testing is defined in the "STS Directory of the  
Swiss Accreditation Service".

To comply with this European Standard RCC is obliged to make the following statements:

- The test results relate only to the items tested.
- Information on the error of measurement (confidence interval, where relevant) can be requested.
- This report shall not be reproduced, except in full, without the written approval of the testing laboratory.



EIDGENÖSSISCHES DEPARTEMENT DES INNERN  
DÉPARTEMENT FÉDÉRAL DE L'INTÉRIEUR  
DIPARTIMENTO FEDERALE DELL'INTERNO

GLP Compliance Statement

It is hereby certified that

on

February 12-16, 1996  
February 19-23, 1996  
June 14, 1996

the testing facilities of

RCC Holding Company Ltd  
4414 Füllinsdorf  
Switzerland

were inspected by the Federal Office of Public Health, the Federal Office of Environment, Forests and Landscape and the Intercantonal Office for the Control of Medicaments with respect to the compliance with the Swiss GLP Principles. The inspection was performed in agreement with the OECD Guidelines for National GLP Inspections and Audits and comprised the following testing facilities:

- RCC Research and Consulting Company Ltd, Itingen
- RCC Umweltchemie AG, Itingen
- RCC Pharamalytics Ltd, Itingen
- BRL Biological Research Laboratories Ltd/Microbiology, Füllinsdorf

It was found that the aforementioned testing facilities were operating in compliance with the Swiss Principles of Good Laboratory Practice (Good Laboratory Practice [GLP] in Switzerland, Procedures and Principles, March 1986) at the time they were inspected.

FEDERAL DEPARTMENT OF THE INTERIOR

A handwritten signature in black ink, appearing to be 'Ruth Dreifuss'.

Bern, July 9, 1996

Ruth Dreifuss  
Federal Councillor